This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (previously amended) A method of modifying a polypeptide, comprising:

a) identifying at least one immunodominant epitope in a polypeptide that has at least one substantial therapeutic activity, wherein the immunodominant epitope is identified by binding of the epitope to an antibody or population of antibodies obtained from a naïve human or animal or population thereof; and

b) modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

2. (previously amended) A method according to claim 1 wherein the polypeptide has an amino acid sequence that has at least 80% sequence identity to a full-length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human or animal.

3. (previously amended) A method according to claim 2, wherein the polypeptide has an amino acid sequence that has about 100% sequence identity to a full-length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human or animal.

4. (original) The method according to claim 1, wherein the polypeptide is selected from the group consisting of human thrombopoietin, growth hormones, cytokines, receptors, and humanized antibodies.

5. (previously amended) A method according to claim 1, wherein the animal is selected from the group consisting of primates, cattle , pigs, poultry, and mice.

6. (original) A method according to claim 1, wherein the modification is a deletion of at least one immunodominant epitope.

7. (original) A method according to claim 1, wherein the modification is a modification of at least one amino acid in the immunodominant epitope by N-glycosylation or pegylation.

8. (original) A method according to claim 1, wherein the modification is a mutation of one or more amino acids in at least one immunodominant epitope.

9. (original) A method according to claim 1, wherein the polypeptide is produced in a non human source.

10-12. (cancelled)

10. (previously amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope in a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding of the epitope to an antibody or population of antibodies from a naive human or animal or population thereof,

b) selecting an immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining the substantial therapeutic activity of the therapeutic polypeptide.

14-21. (cancelled)

22-29. (cancelled)

30. (previously amended) A method of modifying a nucleic acid encoding a modified polypeptide comprising:

a) identifying at least one immunodominant epitope in a polypeptide that has at least one substantial therapeutic activity, wherein the immunodominant epitope is identified by binding of the epitope to an antibody or population of antibodies obtained from a naive human or animal or population thereof;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

31. (currently amended) A host cell comprising ~~the modified isolated nucleic acid of claim 30~~ a nucleic acid comprising a polynucleotide encoding a modified polypeptide, wherein the modified polypeptide has at least one change in an immunodominant epitope of the polypeptide that reduces an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

32-34. (cancelled)

35. (previously amended) A method of modifying a polypeptide, comprising:

a) identifying at least one immunodominant epitope in a polypeptide that has at least one substantial therapeutic activity, wherein the immunodominant epitope is identified by binding of the epitope to an antibody or population of antibodies obtained from a naïve human or population thereof; and

b) modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

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36. (previously presented) A method according to claim 13, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 80% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

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37. (previously presented) A method according to claim 13, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 85% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

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38. (previously presented) A method according to claim 13, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 90% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

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39. (previously presented) A method according to claim 13, wherein the polypeptide is a polypeptide that has an amino acid sequence that has at least 95% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

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40. (previously presented) A method according to claim 13, wherein the polypeptide is an isolated polypeptide that has an amino acid sequence that has about 100% amino acid sequence identity to a full length native sequence or native sequence lacking a signal sequence or an extracellular domain of an endogenous polypeptide in the human.

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41. (previously presented) The method according to claim 13, wherein the polypeptide is selected from the group consisting of human thrombopoietin, growth hormones, cytokines, receptors, and humanized antibodies.

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42. (previously presented) A method according to claim 35, wherein the modification is a deletion of at least one immunodominant epitope.

43. (previously presented) A method according to claim 35, wherein the modification is a modification of at least one amino acid in the immunodominant epitope by N-glycosylation or pegylation.

44. (previously presented) A method according to claim 35, wherein the modification is a mutation of one or more amino acids in at least one immunodominant epitope.

45. (previously presented) A method according to claim 35, wherein the polypeptide is produced in a non human source.

46-48. (cancelled)

49. (previously amended) A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope in a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to an antibody or population of antibodies from a naive human or population thereof,

b) selecting the immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining the substantial therapeutic activity of the therapeutic polypeptide.

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~~50~~. (previously amended) A method of modifying a nucleic acid encoding a modified polypeptide comprising:

a) identifying at least one immunodominant epitope in a polypeptide that has at least one substantial therapeutic activity, wherein the immunodominant epitope is identified by binding to an antibody or population of antibodies obtained from a naive human or population thereof;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

51. (currently amended) A host cell comprising ~~the modified isolated nucleic acid of claim 50~~ a nucleic acid comprising a polynucleotide encoding a modified polypeptide, wherein the modified polypeptide has at least one change in an immunodominant epitope of the polypeptide that reduces an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide, and wherein the immunodominant epitope is identified by binding to an antibody or population of antibodies obtained from a naive human or population thereof.